Pharmacokinetic Modeling and Simulations of Human Anti-C1s Antibody (TNT009) in Normal Human Volunteers and Patients with Complement-Mediated Disorders

B. Jilma[1], J. Gilbert[2], D. Nix[2], C. Chang[3], M. Beliveau[3], and JF Marier[3]

[1]Medical University of Vienna, Austria, [2]True North Therapeutics, Inc., South San Francisco, CA, [3]Certara Strategic Consulting, Montreal, Canada.

Introduction

- TNT009 is a humanized monoclonal antibody (mAb) directed against human complement factor C1s for treatment of the subset of classical pathway (CP)-driven complement-mediated disorders.
- Such conditions are initiated by antibody binding to a target tissue or organ and this, in turn, activates the CP and inflammatory responses responsible for the clinical manifestations of these disorders (Shi et al, 2014).

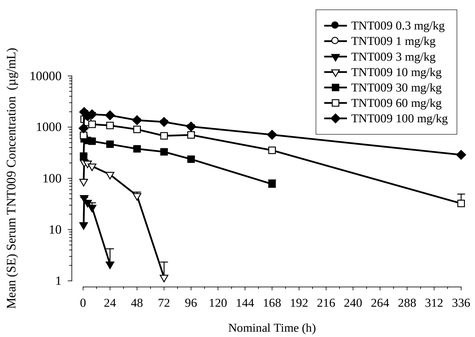
Background

- The objective was to create a PK model that described TNT009 concentrations in male and female normal human volunteers (NHVs) to predict TNT009 exposure following administration of various IV dosing regimens to guide dosing regimens in future clinical trials.

Methods

- Population PK modeling of TNT009 was performed following single dose (0.3 to 100 mg/kg, n=36) and multiple once-weekly doses (30 or 60 mg/kg, n=12) in NHV's and in patients (10 or 60 mg/kg, n=5) with cold agglutinin disease (CAD).
- Modeling and simulations were performed with Phoenix NLME (v.7) with first-order conditional estimation (FOCE) method extended least square algorithm (ELS). Simulations were performed via Monte-Carlo resampling techniques. Usually, 100 replicates of 500 subjects were simulated.
- Following single doses of TNT009, observed PK profiles exhibited target-mediated drug disposition (TMDD; Gabrielsson et al, 2016; Mager et al, 2001), which had an inflection at ~100 µg/mL (**Figure 1**).

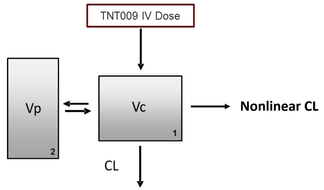
Figure 1: Observed TNT009 Concentrations Following Single Dose of TNT009 in Healthy Volunteers



- An empirical model was constructed, which included a characterization of linear disposition (non-specific), as well as nonlinear components associated to target-specific disposition, as described using traditional Michaelis-Menten kinetics (**Figure 2**).
- This model allowed for an "instantaneous" reading of concentrations of TNT009 to capture the contribution of linear and nonlinear disposition.

Results

Figure 2: Schematic Representation of Population PK Model



CL= Apparent linear clearance; CLd = peripheral clearance; CLnl = apparent non-linear clearance; Vc= Apparent central volume of distribution; Vp= Apparent peripheral volume of distribution.

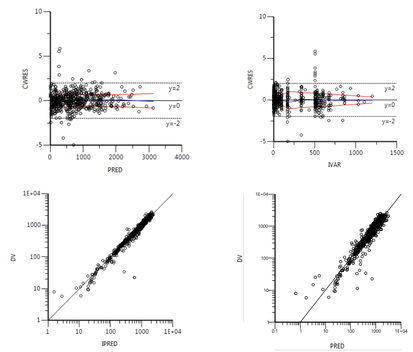
- Target-mediated disposition (TMDD) is expected to increase CL at low doses, and these saturable components of elimination are represented by a Michaelis-Menten equation:

$$CL_{total} = CLlinear + \left(\frac{V_m}{K_m + CTNT_{009}}\right)$$

where CL_{total} is the total clearance, CL_{linear} is the linear clearance (non-specific FcRn receptor-mediated), V_m is the maximum elimination rate (C1s-mediated), K_m is the Michaelis-Menten constant, and C_{TNT009} is the concentrations of TNT009. The model was parameterized with independent random effects (except Vmax, Km and CLd).

Goodness of fit of the population PK model of TNT009 is presented in **Figure 3**.

Figure 3: Model Diagnostics for the Population PK Model Designed to Describe the Normal Healthy Volunteer Data



- The top figures represent the residuals (predicted – observed) vs. population model predicted (PRED) concentrations and time, respectively. Residuals were randomly distributed around 0 with no obvious bias (flat blue line and flat red line).
- The bottom figures represent the individual model (IPRED) and population (PRED) predicted values to the observed values (DV) in log-log scale. Predictions are well correlated to observations as they fall on the identity lines, with little bias at low concentrations due to the TMDD correction within the structural model.
- Overall, the PK model was deemed appropriate to describe the IV concentration-time profiles of TNT009 in NHV and CAD patients.

Results (Cont'd)

Population PK parameters of TNT009 are presented in **Table 1**.

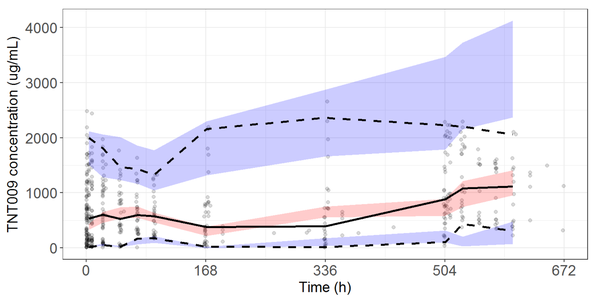
Table 1: Population PK Parameter Estimates in Normal Healthy Volunteers and CAD Patients

Parameters	Population Estimate (%RSE)		%BSV (%RSE)	
CL (mL/h)	5.35	10.8	53.0	10.8
Vc (mL)	3723	3.2	18.8	8.5
CLd (mL/h)	25.0	8.5	NA	NA
Vp (mL)	1349	9.9	72.1	12.8
Km (µg/mL)	6.23	13.7	NA	NA
Vm (µg/h)	9699	2.8	NA	NA
Error Model				
Proportional Error (%)	17.4	14.2	NA	NA
Additive Error (µg/mL)	3.95	8.5	NA	NA

Shrinkage < 42% in all cases; %RSE = percent relative standard error; %BSV = between-subject coefficient of variability; NA = not applicable

- The CL and Vc of TNT009 were 5.35 mL/h (or 0.13 L/day) and 3723 mL, respectively. These values were consistent with the typical CL and Vc reported for other mAbs (i.e., 0.20 L/day and 3610 mL, respectively) based on model-based meta-analysis (Davda et al., 2014).
- Between-subject variability (BSV) on PK parameters ranged from 18.8 to 72.1%.
- The unexplained error was assessed using a proportional (17.4%) and additive (3.95 µg/mL) error terms. The uncertainty (RSE) around parameter estimates was low (<14%).
- The observed linear clearance was consistent with non-compartmental clearance values previously observed at high doses.
- The model resulted in an adequate goodness of fit of TNT009 in healthy volunteers and patients, as assessed by the visual predictive check (VPC) on observed concentrations.

Figure 4: Observed vs Predicted TNT009 concentrations for NHV and CAD Patients



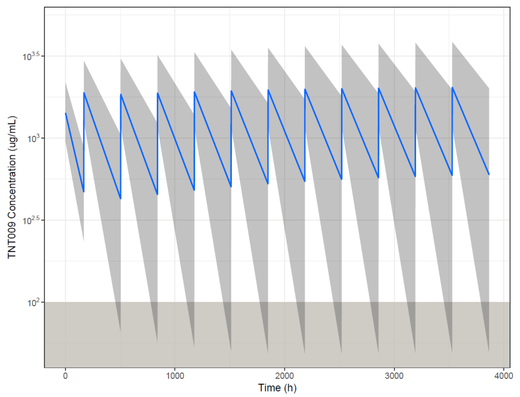
(Black circles = observed values; solid line = 50th percentile; dotted lines = 5th/95th percentiles);
red shaded area = 95% confidence intervals for the 50th percentile;
blue shaded areas = 95% confidence intervals for the 5th/95th percentiles

- As determined from a separate PK/PD analysis (Jilma et al, 2017), serum concentrations of TNT009 required to maintain complete inhibition was reported to range between 20 and 100 µg/mL (determined from IC_{90} and TMDD inflection point estimation).
- Simulations were performed in order to estimate the percent of subjects above each of these target concentrations at doses of 30 mg/kg weekly, 60 mg/kg weekly and a new dose to be tested 75 mg/kg given on Day 0, Day 7 and then every other week.

Results (Cont'd)

- A graph of simulated concentration-time profiles of TNT009 following repeated IV administration of 75 mg/kg is presented in **Figure 5**.

Figure 5: Simulated Median (90% CI) Concentration-Time Profiles Following Repeated Administrations of 75 mg/kg TNT009



Blue line = simulated median TNT009 concentrations; dark grey shaded area = 90% CI for median TNT009 concentrations; light grey shaded area = area below 100 µg/mL threshold

- Concentrations of TNT009 remained above the 100 µg/mL critical threshold, with only a small portion of the 90% CI band falling below this threshold.

Conclusions

- A population PK model built using NHV and patient data adequately described the observed data, including the pronounced TMDD of TNT009.
- Simulations suggest that a 75 mg/kg (QW/Q2W) dose is expected to maintain concentrations of TNT009 above the critical threshold of 100 µg/mL.

References

- Davda JP, Dodds MG, Gibbs MA, Wisdom W, Gibbs J. A model-based meta-analysis of monoclonal antibody pharmacokinetics to guide optimal first-in-human study design. MAbs. 2014 Jul-Aug;6(4):1094-102.
- Gabrielsson J, Weiner D (2016). Pharmacokinetic & Pharmacodynamic Data Analysis: Concepts and Applications (5th Edition). Swedish Pharmaceutical Press, Stockholm, Sweden.
- Jilma B, Gilbert J, Nix D, Chang C, Beliveau M, Marier JF. Pharmacokinetic/Pharmacodynamic Analysis of Human Anti-C1s Antibody (TNT009) and Classical Complement Pathway (CP) Activity. Poster presented at American Society for Clinical Pharmacology and Therapeutics Annual Meeting 2017 Mar 15-18; Washington, DC.
- Mager DE, Jusko WJ. General Pharmacokinetic Model for Drugs Exhibiting Target-Mediated Drug Disposition. J. Pharmacokinet Pharmacodyn, 28 (6); Dec 2001.
- Shi J, Rose EL, Singh A, Hussain S, Stagliano NE, Parry GC, Panicker S. TNT003, an inhibitor of the serine protease C1s, prevents complement activation induced by cold agglutinins. *Blood 2014, 123(26): 4015-4022.*

ASCPT, Washington DC, 17 March 2017

Presentation Number: PII-017